FORM PTO-1390 (Modified) (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

# TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

| ATTORNEY'S DOCKET NUMBER | U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR) |
|---|---|
| 6386-08-IM | 09/889341 |

| INTERNATIONAL APPLICATION NO. | INTERNATIONAL FILING DATE | PRIORITY DATE CLAIMED |
|---|---|---|
| PCT/EP00/01574 | 25 February 2000 | 30 March 1999 |

TITLE OF INVENTION

**METHOD FOR ARYLATING AZA-HETEROCYCLES WITH ACTIVATED AROMATIC COMPOUNDS IN THE PRESENCE OF CESIUM CARBONATE**

APPLICANT(S) FOR DO/EO/US

**BARTH, Hubert; STEINER, Klaus; BETCHE, Hans-Jurgen; SCHNEIDER, Simon; BAYER, Ulrich; WESTERMEYER, Manfred; WOLFSPERGER, Ulrike**

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

**Items 13 to 20 below concern document(s) or information included:**

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☒ Certificate of Mailing by Express Mail
20. ☐ Other items or information:

| U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR) | INTERNATIONAL APPLICATION NO. | ATTORNEY'S DOCKET NUMBER |
|---|---|---|
| 09/889341 | PCT/EP00/01574 | 6386-08-IM |

21. The following fees are submitted:.

**BASIC NATIONAL FEE ( 37 CFR 1.492 (a) (1) - (5)) :**

| | | CALCULATIONS PTO USE ONLY |
|---|---|---|
| ☒ | Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... | **$970.00** |
| ☐ | International preliminary examination fee (37 CFR 1.482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO ..... | **$840.00** |
| ☐ | International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... | **$690.00** |
| ☐ | International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... | **$670.00** |
| ☐ | International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) ..... | **$96.00** |

**ENTER APPROPRIATE BASIC FEE AMOUNT =** **$970.00**

Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)). **$0.00**

| CLAIMS | NUMBER FILED | NUMBER EXTRA | RATE | |
|---|---|---|---|---|
| Total claims | 5 - 20 = | 0 | x $18.00 | **$0.00** |
| Independent claims | 2 - 3 = | 0 | x $80.00 | **$0.00** |
| Multiple Dependent Claims **(check if applicable).** | | | ☒ | **$260.00** |

**TOTAL OF ABOVE CALCULATIONS =** **$1,230.00**

Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable).** ☐ **$0.00**

**SUBTOTAL =** **$1,230.00**

Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). + **$0.00**

**TOTAL NATIONAL FEE =** **$1,230.00**

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐ **$0.00**

**TOTAL FEES ENCLOSED =** **$1,230.00**

**Amount to be: refunded** $

**charged** $

☐ A check in the amount of to cover the above fees is enclosed.

☒ Please charge my Deposit Account No. **23-0455** in the amount of **$1,230.00** to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **23-0455** A duplicate copy of this sheet is enclosed.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO:

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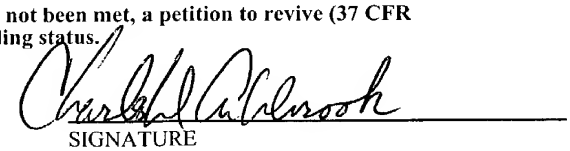

SIGNATURE

**Charles W. Ashbrook**

NAME

**27,610**

REGISTRATION NUMBER

**16 July 2001**

DATE

09/889741 #2

SCANNED

JC12 Rec'd PCT/PTO 16 JUL 2001

| CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10)<br>Applicant(s): **Hubert Barth, et al.** | | | Docket No.<br>**6386-08-IM** |
|---|---|---|---|
| Serial No. | Filing Date | Examiner | Group Art Unit |

Invention: **METHOD FOR ARYLATING AZA-HETEROCYCLES WITH ACTIVATED AROMATIC COMPOUNDS IN THE PRESENCE OF CESIUM CARBONATE**

I hereby certify that the following correspondence:

**Application for filing under 35 U.S.C. 371**

*(Identify type of correspondence)*

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: The Assistant Commissioner for Patents, Washington, D.C. 20231

**July 16, 2001**
*(Date)*

**Cindy Malocha**
*(Typed or Printed Name of Person Mailing Correspondence)*

Cindy Malocha
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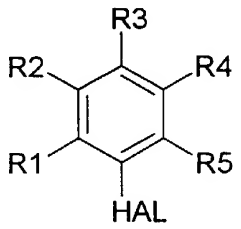
GÖDECKE AKTIENGESELLSCHAFT



# Process for the arylation of aza-heterocycles with activated aromatics in presence of caesium carbonate

## Description

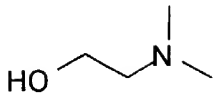
The subject of the invention is a process for the nucleophilic substitution on activated aromatics of the general formula XIV



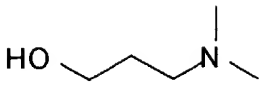

XIV

in which R1, R2, R3, R4 and R5 are the same or different and signify a hydrogen atom, a nitro group, a cyano group, an alkoxycarbonyl group with up to 5 C-atoms, an aldehyde group, an alkylearbonyl group with up to 5 C-atoms, an arylcarbonyl group or an amide group, whereby the radicals R1 to R5 cannot all simultaneously be a hydrogen atom and HAL stands for a halogen atom but especially for a fluorine atom, with nucleophils, such as alcohols, amines, sulphoximides, CH-acidic compounds of the formulae V to XI

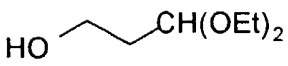
Figure 1



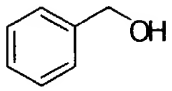

V



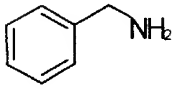

VI



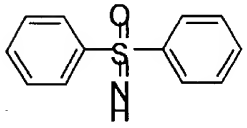

VII



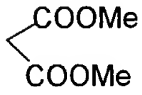

VIII




IX

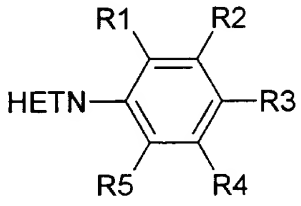



X




XI

in dipolar aprotic solvents, especially dimethylformamide, with use of caesium. carbonate.
The process is preferred for the preparation of compounds of the general formula I




I

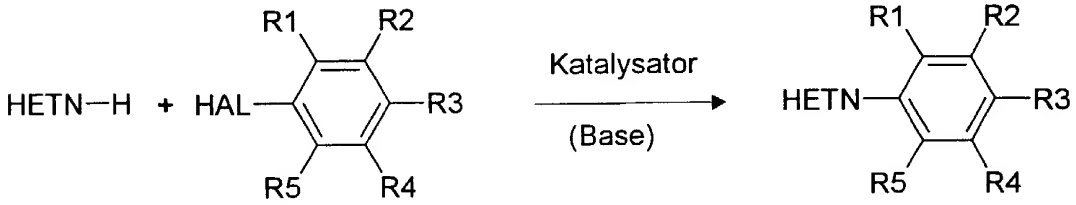
in which HETN signifies an aromatic aza-heterocycle with, in all, 5 or 6 ring atoms, whereby up to 3 ring atoms can be nitrogen atoms, and up to two further aromatic carbon rings can be condensed on to the heterocycle and R1 to R5 have the above-mentioned meaning.

Compounds of the general formula I play an important part in medicinal chemistry. Thus, e.g. one finds the

N-aryl-aza-heterocyclic structure in substances with anti-oestrogenic (E. Angerer, J. Strohmeier, J. Med. Chem. 30, 131, 1987), with analgesic (E.J. Glamkowski et al., J. Med. Chem. 28, 66, 1985), with anti-diabetic (R.B. Chapleo, G.P. Fagan, Ann. Drug 5 Data Rep. 15, 59, 1993), with anti-miciobial (A.G. Kamat, G.S. Gadaginamath, Indian J. Chem., Sect. B, 33, 255, 1994), with neuroleptic (J. Perregaard et al., J. Med. Chem. 35, 1092, 1.992), with anti-allergic (P. Ungast et al., J. Med. Chem. 32, 1360, 1989), with angiotensin-antagonistic (S.R. Stabler and Jahangir, Syn. Commun. 24, 123, 1994) and with PDGF receptor inhibitory action (Brian D. Palmer et al., J. Med. Chem. 41, 5457, 1998).

Compounds of the general formula I can be prepared according to various methods. A frequently used method consists in the reaction of aza-heterocycles with activated aryl halides in the presence of catalysts and/or bases or, in few cases, also without further additives, according to scheme 1:

Schema 1




I

Thus, e.g. 1-(benzotriazol-1-yl)-2,4-dinitro-benzene can be obtained in 96% yield by 9 days boiling of benzotriazole in toluene (A.R. Katritzky, J. Wu, Synthesis 1994, 597).

4-Heterocyclicly-substituted nitrobenzenes and benzaldehydes can be obtained by reaction of the particular aza-heterocycles, such as e.g. benzotriazole, 1,2,4-triazole

or benzimidazole, with 4- fluorobenzaldehyde or 4-fluoro- or 4-chlorobenzaldehyde in DMSO or DMF at 100°C (D.J. Gale, J.F.K. Wilshire, Aust. J. Chem. 23, 1063, 1970; J. Rosevear, J.F.K. Wilshire, Aust. J. Chem. 44, 1097, 1991).

Nitrophenylazoles can be prepared by Ullmann condensation of azoles with aryl halides in pyridine in the presence of potassium carbonate and copper (II) oxide at high temperatures and long reaction times (M.A. Khan, J.B. Polys, J. Chem. Soc. (C), 1970, 85; A.K. Khan, E.K. Rocha, Chem. Pharm. Bull. 25, 3110, 1977) or, however, by reaction of azoles with suitable fluoronitrobenzenes in DMSO at comparatively high temperature and in the presence of potassium carbonate (M.F. Mackay, G.J. Trantino, J.F. Wilshire, Aust. J. Chem. 46, 417, 1993).

1-Arylindoles with activating substituents in the aryl part were obtained by reaction of indole with activated aryl halides in the presence of 37% $KF/Al_2O_3$ and catalytic amounts of crown ethers in DMSO at 120°C (W.J. Smith, J. Scott Sawyer, Tetrahedron Lett. 37, 299, 1996).

There is also described the arylation of azoles with activated aryl halides in the presence of bases, such as caesium carbonate and sodium tert.-butylate, whereby, however, the presence of palladium catalysts is additionally necessary and the reaction itself requires high temperatures (65° to 120°C) and long reaction times (3 to 48 hours) (G. Mann, J.F. Hartwig, M.D. Driver, C. Fernandez-Rivas, J. Am. Chem. Soc. 120, 827, 1998; I.P. Beletskaya, D.V. Davydov, M. MorenoManas, Tetrahedron Lett. 39, 5617, 1998).

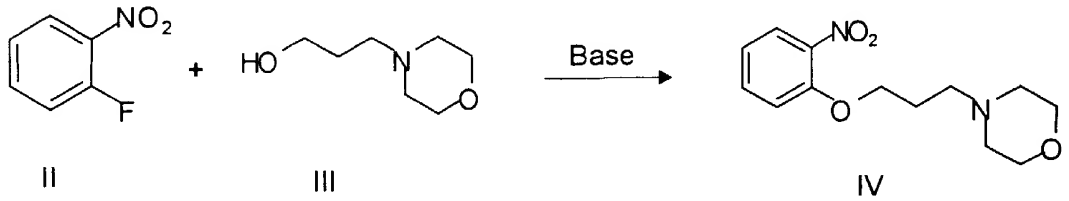
The use of caesium carbonate as reagent in the case of carbon-heteroatom coupling reactions is also known but further special catalysts must additionally always be used in

such reactions (Christopher G. Frost, Paul Mendonca, J. Chem. Soc., Perkin Trans. 1, 1998, 2615).

In general, from the above-given examples, it can be deduced that for arylations of azoles with activated aryl halides, relatively drastic conditions, such as high temperatures, long reaction times, as well as special catalysts, are frequently necessary.

In connection with the synthesis of a potentially anti-cancer compound, the reaction was investigated by use of morpholinopropanol (III) with o-nitrofluorobenzene (II) (scheme 2):

Scheme 2



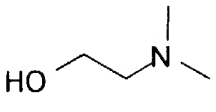

II III IV

Based on our experience with the system caesium carbonate/dimethylformamide for the preparation of carbonates from alcohols and alkyl/aryl halides (DE 199 05 222.0) and of heterocyclic carbamates from aza-heterocycles and alkyl/aryl halides, we investigated whether this system is also suitable for the above reaction.

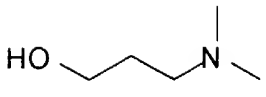
Surprisingly, it was found that this reaction leads at 23°C within 48 hours to the desired product (IV) in 82% yield.

On the basis of this finding, it was now investigated whether other nucleophils, such as e.g. the nucleophils V to X also react with 2-fluoronitrobenzene at room temperature in the system caesium carbonate/dimethylformamide:

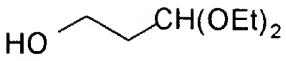
Figure 1



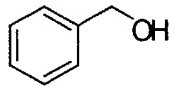

V



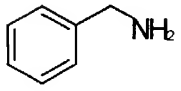

VI



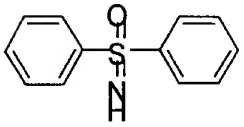

VII



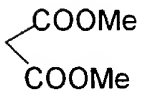

VIII




IX



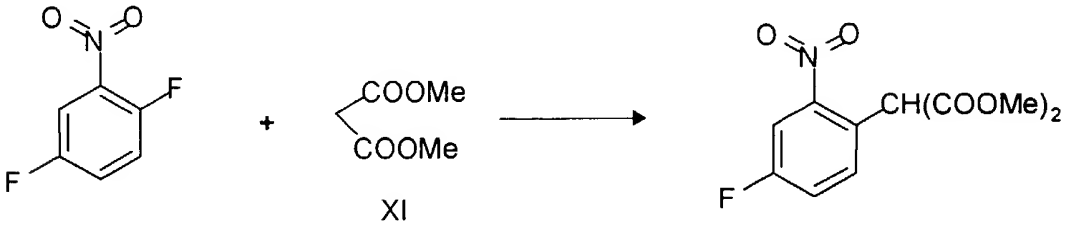

X




XI

It was found that these reactions also give the desired products in good to very good yield at room temperature within 24 to 64 hours. The reaction of 2,5-difluoronitrobenzene (XII) with malonic acid dimethyl ester (XI) at room temperature in the system caesium carbonate/dimethylformamide also leads after 24 hours in 98% yield to the desired product XIII (scheme 3):

Scheme 3

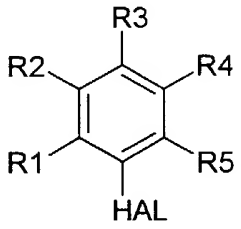



XII XI XIII

The preparation of compound XIII is described in the literature with use of sodium hydride in dimethyl sulphoxide

at 100°C in 96% yield (Li Sun et al., J. Med. Chem. 41, 2588, 1998).

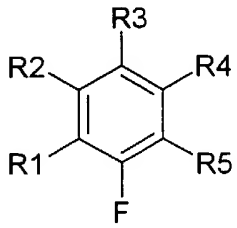
Encouraged by these results, the arylation of aza-heterocycles with activated aromatics of the general formula XIV




XIV

in which $R^1$ to $R^5$ have the above-given meaning and HAL stands for a halogen atom but especially for a fluorine atom, was investigated in the system caesium carbonate/ dimethylformamide.

Surprisingly, it was found that almost all azaheterocycles used already react at room temperature in the presence of caesium carbonate/dimethylformamide with activated fluoroaromatics of the general formula XV to give compounds of the general formula I




XV

Instead of dimethylformamide, there can also be used other dipolar aprotic solvents, such as e.g. dimethylacetamide, acetonitrile, dimethylsulphoxide, acetone or

N-methylpyrrolidone; however, the reaction times at room temperature are then distinctly longer and the yields often lower.

The process procedure in the case of the preparative carrying out of the arylation is very simple. One dissolves equimolar amounts of azaheterocycle and activated aromatics of the general formula XIV but especially of the general formula XV at room temperature in a suitable dipolar aprotic solvent, especially dimethylformamide, adds thereto a 2 to 4 molar excess of anhydrous caesium carbonate and stirs at room temperature until the reaction is ended. The reaction is monitored by means of thin layer chromatography. In the case of less reactive aromatics, in a few cases the reaction temperature must be increased to about 80°C.

At the end of the reaction, one pours the suspension on to water, extracts the product with ethyl acetate and purifies the product obtained after ev;~poration of the organic phase with the methods usual in organic chemistry, e.g. by crystallisation or chromatography.

The invention is illustrated and explained by the following embodimental examples:

**Example 1**

2-Morpholinopropyloxynitrobenzene

0.57 g 2-fluoronitrobenzene, 0.65 g morpholino-propanol., 3.0 g caesium carbonate and 30 ml dimethylformamide are stirred for 2 days at room temperature in a closed 50 ml round-bottomed flask. One pours the suspension on to 50 ml water, extracts the aqueous phase 3 times with, in each case, 50 ml ethyl acetate and evaporates the combined organic phases on a rotavapor. For the removal of the dimethylformamide, which would disturb the chromatographic

separation, the DMF-containing residue is again evaporated 2 to 3 times, together with some toluene, at 50°C and 30 mbar vacuum. The oily residue is then purified on silica gel (0.04 to 0.063 mm) at 0.1 bar by flash chromatography. One obtains 0.9 g of oil (82.4%).

The following Examples were carried out analogously to Example 1, there are given the following reaction parameters (reaction time/eluent for chromatography/yield/physical statements):

**Example 2**

2-Dimethylaminoethyloxynitrobenzene
from 2-fluoronitrobenzene and 2-dimethylaminoethanol
64 h/toluene-ethanol 10+2/91.8%/oil

**Example 3**

2-Dimethylaminopropyloxynitrobenzene
from 2-fluoronitrobenzene and 3-dimethylaminopropanol-
h/methylene chloride-methanol
10 + 2/58.7%/oil

**Example 4**

2-(3,3-Diethoxypropoxy)-nitrobenzene
from 2-fluoronitrobenzene and 3-hydroxypropionaldehyde
diethyl acetal
64 h/hexane-ethyl acetate 10+2/83.7%/oil

**Example 5**

2-Benzyloxynitrobenzene
from 2-fluoronitrobenzene and benzyl alcohol
24 h/toluene/95.7%/oil

**Example 6**

2-Benzylaminonitrobenzene

from 2-fluoronitrobenzene and benzylamine
64 h/hexane-ethyl acetate 10+2/42.7%/m.p. 74°C

**Example 7**

4-Fluoro-2-nitrophenylmajonic acid dimethyl ester from
2,5-difluoronitrobenzene and malonic acid dimethyl ester
24 h/toluene-ethanol 10+0.5/98%/oil

**Example 8**

N-2-Nitrophenyldiphenyl sulphoximide
from 2-fluoronitrobenzene and diphenyl sulphoximide
48 h/toluene-ethanol 10+2/72%/m.p. 158°C

**Example 9**

N-2-cyanophenyldiphenyl sulphoximide
from 2-fluorobenzonitrile and diphenyl sulphoximide at 80°C
8 h/toluene-ethanol 10+1/74.3%/m.p. 160°C

**Example 10**

N-4-Cyanophenyldiphenyl sulphoximide
from 4-fluorobenzonitrile and diphenyl sulphoximide
64 h/toluene-ethanol 10+1/61.2%/m.p. 159°C

**Example 11**

N-4-Nitrophenyldiphenyl sulphoximide
from 4-fluoronitrobenzene and diphenyl sulphoximide
64 h/toluene-ethanol 10 + 0.5/64.1%/m.p. 166°C

**Example 12**

1-(2-Nitrophenyl)-indole
from 2-fluoronitrobenzene and indole
24 h/hexane-ethyl acetate 10+2/90%/81°C

**Example 13**

1-(4-Cyanophenyl)-pyrrole

from 4-fluorobenzonitrile and pyrrole at 80°C
8 h/toluene/84.1%/105°C

**Example 14**

1-(4-Cyanophenyl)-pyrrole
from 4-fluorobenzonitrile and pyrrole (room temperature)
64 h/toluene/toluene/39.1%/103 - 104°C

**Example 15**

1-(4-Cyanophenyl)-indole
from 4-fluorobenzonitrile and indole
64 h/toluene-ethanol 10+1/100%/93 - 94°C

**Example 16**

1-(4-Ethoxycarbonylphenyl)-indole
from 4-fluorobenzoic acid ethyl ester and indole at 80°C
8 h/hexane-ethyl acetate 10 + 2/77.2%/m.p. 51°C

**Example 17**

1-(2-methoxycarbonylphenyl)-indole
from 2-fluorobenzoic acid methyl ester and indole
64 h/toluene/20%/oil

**Example 18**

1-(4-Nitrophenyl)-indole
from 4-fluoronitrobenzene and indole
64 h/toluene/98%/m.p. 134°C

**Example 19**

1-(2-Nitrophenyl)-indole-5-carboxylic acid methyl ester
from 2-fluoronitrobenzene and indole-5-carboxylic acid methyl ester
64 h/toluene-ethanol 10+1/98%/m.p. 89°C

**Example 20**

1-(2-nitrophenyl)-indole-3-carboxylic acid methyl ester
from 2-fluoronitrobenzene and indole-carboxylic acid methyl ester 24 h/toluene-ethanol 10+1/96%/m.p. 155°C

**Example 21**

1-(2-Nitrophenyl)-indole-3-carbonitrile
from 2-fluoronitrobenzene and indole-3-carbonitrile
24 h/toluene-ethanol 10+1/98%/m.p. 151°C

**Example 22**

1-(Benzotriazol-1-yl)-2,4-dinitrobenzene
from fluoro-2,4-dinitrobenzene and benzotriazole
24 h/toluene-ethanol 10+1/85.5%/m.p. 185°C

**Example 23**

1-(Benzotriazol-1-yl)-2,4-dinitrobenzene
from chloro-2,4-dinitrobenzene and benzotriazole
24 h/toluene-ethanol 10+1/85.5%/m.p. 185°C

**Example 24**

1-(4-Nitrophenyl)-indole-3-aldehyde from
4-fluoronitrobenzene and indole-3-aldehyde
24 h/crystallisation in the case of working up/91.6%/ m.p. 269°C

**Example 25**

1-(4-Formylphenyl)-indole
from 4-fluorobenzaldehyde and indole
48 h/toluene/7.7%/oil

**Example 26**

1-(2-Methoxycarbonylphenyl)-indole
from 2-fluorobenzoic acid methyl ester and indole at 80°C
8 h/hexane-ethyl acetate 10+2/19.4%/oil

**Example 27**

5-Methyl-1-(4-nitrophenyl)-indole
from 4-fluoronitrobenzene and 5-methylindole
24 h/toluene/77.3%/m.p. 147°C

**Example 28**

5-Nitro-1-(4-nitrophenyl)-indole
from 4-fluoronitrobenzene and 5-nitroindole
24 h/crystallisation in the case of working up/86.9%/m.p. 235°C

**Example 29**

5-Chloro-1-(2-nitrophenyl)-indole
from 2-fluoronitrobenzene and 5-chloroindole
24 h/toluene/71.5%/m.p. 142°C

**Example 30**

5-Methoxy-L-(2-cyanophenyl)-indole
from 2-fluorobenzonitrile and 5-methoxyindole
3 h/toluene/100%/m.p. 99°C

**Example 31**

1-(2-Nitrophenyl)-pyrrole
from 2-fluoronitrobenzene and pyrrole
64 h/hexane-ethyl acetate 10+2/68.6%/m.p. 105°C

**Example 32**

5-Methoxy-1-(4-nitrophenyl)-indole
from 4-chloronitrobenzene and 5-methoxyindole at 80°C
8 h/toluene/27.2%/m.p. 187°C

**Example 33**

3-Methyl-1-(4-nitrophenyl)-indole
from 4-fluoronitrobenzene and 3-methylindole
24 h/toluene/84.1%/m.p. 146°C

**Example 34**

5-Methoxy-1-(4-ethoxycarbonylphenyl)-indole
from 4-fluorobenzoic acid ethyl ester and 5-methoxyindole at 80°C
8 h/hexane-ethyl acetate 10 + 2/68.5%/oil

**Example 35**

5-Methoxy-1-(4-nitrophenyl)-indole
from 4-fluoronitrobenzene and 5-methoxyindole
18 h/crystallisation in the case of working up/88.1%/ 5 m.p. 188°C

**Example 36**

1-(2-Nitrophenyl)-indole-2-carboxylic acid ethyl ester
from 2-fluoronitrobenzene and indole-2-carboxylic acid ethyl ester
58 h/toluene/47.9%/m.p. 90°C

**Example 37**

1-(4-Nitrophenyl)-indole-2-carboxylic acid ethyl ester
from 4-fluoronitrobenzene and indole-2-carboxylic acid ethyl ester at 80°C
8 h/toluene/78.5%/m.p. 135°C

**Example 38**

1-(3-Nitrophenyl)-indole from
3-fluoronitrobenzene and indole at 80°C
6 h/hexane-ethyl acetate 10+2/72.9%/m.p. 66°C

**Example 39**

1-(3-Cyanophenyl)-indole
from 3-fluorobenzonitrile and indole at 80°C
8 h/toluene-ethanol 10+1/55.8%/m.p. 37°C

**Example 40**

1-(2-Cyanophenyl)-indole

from 2-fluorobenzonitrile and indole

64 h/toluene/100%/m.p. 112°C

**Example 41**

1-(2-Nitrophenyl)-imidazole

from 2-fluoronitrobenzene and imidazole

18 h/toluene-ethanol 10+2/92%/m.p. 98° - 99°C

**Example 42**

1-(2-Nitrophenyl)-benzimidazole

from 2-fluoronitrobenzene and benzimidazole

18 h/toluene-ethanol 10+2/98.8%/oil

**Example 43**

1-(4-Nitrophenyl)-indazole

from 4-fluoronitrobenzene and indazole

18 h/crystallisation in the case of working up/92%/ m.p. 166°C

**Example 44**

N-2,4-Dibitrophenylcarbazole

from 2,4-dinitrofluorobenzene and carbazole

18 h/crystallisation in the case of working up/m.p. 189°C

**Example 45**

1-(2-Cyanophenyl)-1,2,3-triazole

from 2-fluorobenzonitrile and 1,2,3-triazole

24 h/toluene-ethanol 10+1/14.2%/m.p. 112°C

**Example 46**

4-(4-Cyanophenyl)-1,2,4-triazole

from 4-fluorobenzonitrile and 1,2,4-triazole

24 h/toluene-ethanol 10+2/14.2%/m.p. 169°C

**Example 47**

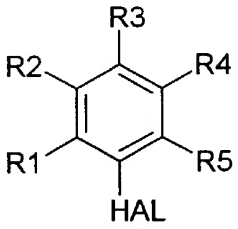
5-Chloro-1-(2-cyanophenyl)-indole
from 2-fluorobenzonitrile and 5-chloroindole
2 h/toluene/70.4%/m.p. 129 - 130°C

**Example 48**

1-(2-Pyridyl)-indole
from 2-fluoropyridine and indole at 80°C
24 h/toluene/84.1%/m.p. 58°C.

## Patent Claims

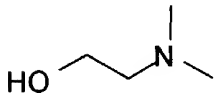
1. Process for the nucleophilic substitution on activated aromatics of the general formula XIV



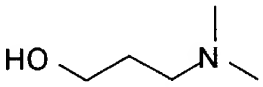

XIV

in which R1, R2, R3, R4 and R5 are the same or different and signify a hydrogen atom, a nitro group, a cyano group, an alkoxycarbonyl group with up to 5 C atoms, an aldehyde group, an alkylcarbonyl group with up to 5 C-atoms, an arylcarbonyl group or an amide group, whereby the radicals R1 to R5 cannot all simultaneously be a hydrogen atom and HAL stands for a halogen atom, with nucleophils, such as alcohols, amines, sulphoxides, CH-acidic compounds of the formulae V to XI

Figure1




V

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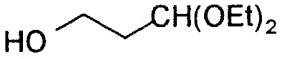


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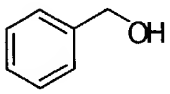
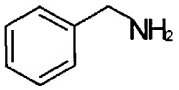
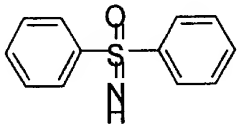


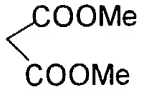

VIII




IX



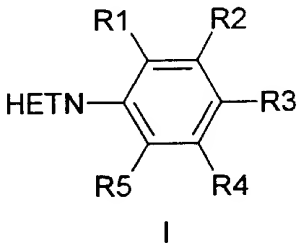

X




XI

in dipolar aprotic solvents in the presence of caesium carbonate at room temperature.

2. Process according to claim 1 for the preparation of compounds of the general formula I




I

in which HETN signifies an aromatic aza-heterocycle with, in all, 5 or 6 ring atoms, whereby up to 3 ring atoms can be nitrogen atoms and up to two further aromatic carbon rings can be condensed on to the heterocycle and R1, R2, R3, R4 and R5 have the above given meaning.

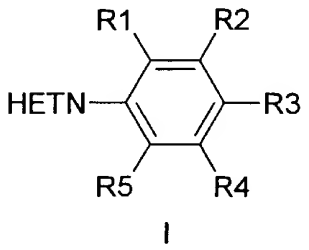
3. Process according to claim 1 or 2, characterised in that the solvent is acetone, acetonitrile, dimethyl-sulphoxide, dimethylacetamide, N-methylpyrrolidone or dimethylformamide.

4. Process according to claim 1 or 2, characterised in that the solvent is dimethylformamide.

5. Process according to claim 1 or 2, characterised in that HAL in the general formula XIV is a fluorine atom.

## Summary

The invention concerns a process for the preparation of N-aryl-aza-heterocycles of the general formula I




I

by reaction of aza-heterocycles with activated aryl halides with use of caesium carbonate without addition of further catalysts at room temperature.

Docket No.
6386-08-IM

# Declaration and Power of Attorney For Patent Application

## English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METHOD FOR ACYLATING AZA-HETEROCYCLES WITH ACTIVATED AROMATIC COMPOUNDS IN THE PRESENCE OF CESIUM CARBONATE

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on _____ As United States Application No. _____ or PCT International Application Number _____
and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

| Prior Foreign Applications | | | Priority Not Claimed |
|---|---|---|---|
| 19914610.1 (Number) | Germany (Country) | 30MR1999 (Day/Month/Year Filed) | ☐ |
| (Number) | (Country) | (Day/Month/Year Filed) | ☐ |
| (Number) | (Country) | (Day/Month/Year Filed) | ☐ |

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

| (Application Serial No.) | (Filing Date) |
|---|---|
| (Application Serial No.) | (Filing Date) |
| (Application Serial No.) | (Filing Date) |

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

| (Application Serial No.) | (Filing Date) | (Status) (patented, pending, abandoned) |
|---|---|---|
| PCT/EP00/01574 | 25FE2000 | pending |
| (Application Serial No.) | (Filing Date) | (Status) (patented, pending, abandoned) |
| (Application Serial No.) | (Filing Date) | (Status) (patented, pending, abandoned) |

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORINEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (*list name and registration number)*

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